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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,704	02/27/2001	G. Scott Herron	464363000300	5424

7590 03/27/2003
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EXAMINER

BERTOGLIO, VALARIE E

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 03/27/2003

3

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/905,704

Applicant(s)

HERRON, G. SCOTT

Examiner

Valarie Bertoglio

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-30 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 February 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Specification

The disclosure is objected to because of the following informalities: The specification refers to Figure 6B (page 20, lines 9 and 11). However, Figure 6B is not present in the application.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-24, 26, 27, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vivo assay system comprising a composition of microvascular endothelial cells and an immune suppressed non-human-host and methods of using said system to screen compounds for modulation of angiogenesis, does not reasonably provide enablement for an in vivo assay system comprising a composition of microvascular endothelial cells and an immune competent non-human-host and methods of using said system to screen compounds for modulation of angiogenesis. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims are directed to an assay system comprising a composition of telomerized microvascular cells and a non-human host and methods of using the system to assay the effects of compounds on in vivo neovascularization of the cells upon xenografting into the host. The claims, with the exception of claim 8, 25 and 28, encompass any non-human host. Claims 8, 25 and 28 limit the non-human host to an immune suppressed SCID mouse.

The specification fails to enable making and using the claimed in vivo assay system comprising a non-human host that is not immune suppressed. The art at the time of filing held that xenografts are rejected by the host immune system unless the host immune system is suppressed (Gorcynski, WO 99/24565, specifically page 1, lines 15-17). Immune system suppression can be attained through the use of drugs or can be attained by genetic means, take for example, the immune deficient SCID mouse that has been highly utilized for experimentation involving xenografts (refer to Pober, 1997, USPN 5,602,305).

The specification teaches how to carry out the claimed invention using SCID mice as a non-human host. The specification fails to teach how to graft human cells into a non-human host without suppressing the host immune system to prevent graft rejection. It would require one of skill in the art at the time of filing, undue experimentation to determine how to transplant human microvascular endothelial cells into a non-human host wherein the host is not immune suppressed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-10,15-21,24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas (January 2000, Nature Biotech. Vol. 18, pages 39-42) in view of Yang (1999, Jour. Biol. Chem., Vol. 274, pages 26141-26148) as evidenced by Okabe (1997, FEBS Letters, Vol. 407, 313-319) and Bunk (2001, The Scientist, Vol. 15, page 21).

Thomas taught the xenotransplantation of primary bovine adrenocortical cells transfected with human telomerase reverse transcriptase and a GFP reporter gene (page 39, col.2, paragraph 2, lines 1-6) into SCID mice (page 40, col. 2, lines 4-5) and determining the cell proliferation rate of the grafted cells using a stably transformed SV40 large T-antigen as a marker of the cells (page 41, column 2, lines 31-33). Thomas also transplanted cells expressing FGF along with the adrenocortical cells (page 42, col. 1, "Cell transplantation", lines 1-3). Thomas did not teach using human dermal microvascular endothelial cells or adding apoptotic inducers to the xenotransplant or detecting neovascularization in the graft.

However, Yang teaches the telomerization of human dermal microvascular endothelial cells in vitro and the addition of apoptotic inducers to the cells (page 26146, column 1). Yang does not teach grafting the cells into a SCID mouse, adding FGF to the cells, or monitoring cell proliferation using a transformed genetic marker.

It would have been obvious to one of skill in the art at the time the invention was made to combine the teaching of Thomas and Yang and transplant telomerized microvascular endothelial cells expressing a detectable marker gene and treated with various agents into a SCID mouse. One would have been motivated to combine the teachings of Thomas and Yang to observe the effect of various compounds on neovascularization by the microvascular endothelial cells in vivo as it is well known in the art that human dermal microvascular endothelial cells can form vessels upon in vivo transplantation (Yang, page 26148, column 1,

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lines 8-13). Furthermore, because the cells of Thomas comprise a GFP marker gene, it would be obvious to observe the transplanted cells using a fluorescence digital imaging device because it was a well accepted and utilized method as evidenced by Okabe. Okabe generated mice expressing GFP in all tissues for the use of easy visualization using a fluorescence digital imaging device following cellular transplantation (page 313, col. 2, section 2.3 and page 319). It would also have been obvious to use Matrigel in the xenograft because it was a well-established and standard technique to use Matrigel in xenografts (refer to Bunk). Thus, Applicants' claimed invention, as a whole is *prima facie* obvious in the absence of evidence to the contrary.

2) Claims 11,12,14,22 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas in view of Yang as applied to claims 1-10,15-21,24 and 25 above, and further in view of Prewett (1999, Cancer Research, Vol. 59, pages 5209-5218).

Thomas and Yang, as described above, taught an assay system and a method for analyzing the effect of a compound on microvascular endothelial cells grafted into a SCID mouse. Thomas and Yang did not teach specifically using VEGF as a test compound.

However, Prewett taught that VEGF has potent angiogenic and mitogenic activities (page 5209, col. 1, lines 3-7). Prewett grafted Matrigel supplemented with VEGF and FGF, which would normally stimulate neovascularization of the graft, into mice and tested the ability of anti-Flk-1 mAb DC101, which is a VEGF receptor antagonist, to inhibit neovascularization. Furthermore, Prewett demonstrated that by blocking the VEGF receptor with anti-Flk-1 mAb, there was decreased vessel density in tumor xenografts (page 5214, col. 1, lines 3-5).

It would have been obvious for one of skill in the art to use VEGF in the instant invention as it is well known to stimulate vascularization. One would be motivated to combine the teachings of Prewett with those of Thomas and Yang as adding VEGF to the xenografts is likely

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to increase the formation of vascular tissues from the grafted cells. Thus, Applicants' claimed invention, as a whole is *prima facie* obvious in the absence of evidence to the contrary.

3) Claims 13 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas and Yang as applied to claims 1-10, 15-21, 24 and 25 above, and further in view of Ueno (1997, Arter. Thromb. Vasc. Biol., Vol. 17, pages 2453-2460).

Thomas and Yang, as described above, taught an assay system and a method for analyzing the effect of a compound on microvascular endothelial cells grafted into a SCID mouse. Thomas and Yang did not teach specifically using FGF-2 as a test compound.

However, Ueno taught that FGF-2 has potent angiogenic activity in vivo (Introduction, last 3 lines). Ueno grafted FGF-2 expressing cells into mice and observed the induction of functional arteriole formation.

It would have been obvious for one of skill in the art to use FGF-2 in the instant invention as it is well known to stimulate vascularization. One would be motivated to combine the teachings of Ueno with those of Thomas and Yang as adding FGF-2 to the xenografts of the instant invention is likely to increase the formation of vascular tissues from the grafted cells. Thus, Applicants' claimed invention, as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

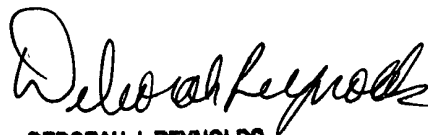
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for

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the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Patent Examiner



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